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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,529	11/15/2001	Audrey Goddard	P2730P1C33	1269

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,529	GODDARD ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-126 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-126 and 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

The Amendments submitted 20 January 2006, have been entered. Claims 1-118, 127 and 128 are canceled.

In view of the papers filed 20 January 2006, the inventorship in this nonprovisional application has been changed by the deletion of: Timothy A. Stewart.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Claims 119-126 and 129-131 are under examination in the Instant Application.

The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior Office action.

Maintained Objections and/or Rejections

35 U.S.C. § 101/112, first paragraph-, Lack of Utility, Enablement.

Claims 119-126 and 129-131 are rejected under 35 U.S.C. 101, as lacking utility. The reasons for this rejection under *35 U.S.C. § 101* are set forth at pages 4-8 of the previous Office Action (26 September 2005). Claims 119-126 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a

specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Action (26 September 2005), one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue (*Remarks/Arguments*, 23 June 2005, page 6 and throughout) that the data presented in the instant Specification are enabling for the nucleic acid of SEQ ID NO: 356 and the claimed polypeptide of SEQ ID NO: 357. They argue that the PRO1182 nucleic acid is a diagnostic marker for lung tumor tissues and point to the results of the gene amplification assay (pages 3 and 8, 20 January 2006; see table 9C of Specification) and the glucose/FFA assay (page 530, Specification).

Applicant's arguments (20 January 2006) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the specification provides data showing an indeterminate increase in chromosome number in 3 cancerous lung tumor tissues out of 12 lung tumor tissues tested (see Table 9C). However, there is no evidence regarding whether or not PRO1182 mRNA or polypeptide levels are reliably increased or decreased in a cancer. Furthermore, as discussed in the previous Office Action (26 September 2005, page 9), what is often seen is a *lack* of correlation between gene amplification and increased peptide levels (Pennica, et al, 1998, Proc. Natl. Acad. Sci., 95: 14717-14722). As discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on *small* changes in transcript gene amplification levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal

of Proteome Research 2: 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean gene amplification level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene amplification and a known role in the disease. However, among genes with a 10-fold or more change in gene amplification level, there was a strong and significant correlation between gene amplification level and a published role in the disease (see discussion section). Regardless of whether there is a correlation between mRNA and protein levels in a sample, the data presented in the instant Application do not show a consistent positive response since only one measurement was made and positive results were found in a minority of cancers.

Given the small increase in gene amplification of PRO1182, in 3 samples of cancer, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a small increase or decrease in gene amplification would correlate with experimentally significant increased or decreased mRNA or polypeptide levels. Further research is necessary to determine whether the small increase in PRO1182 chromosome number in a minority of lung cancer tissues supports a role for the DNA in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention

> with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
>
> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the Specification's assertions that the claimed PRO1182 nucleic acids have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

There is no evidentiary support that PRO1182 is involved in the etiology of cancer in the three samples disclosed in the instant Application. Furthermore, as noted above, the increase in PRO1182 DNA in only some samples of one cancerous tissue, and then displaying merely a two-fold increase, points away from its role in a disease. At any rate, 9 negative results combined with three positive results is too incomplete a study to make a conclusion about PRO1182 and cancer. In additions, the *specific* function of the PRO1182 polypeptide has not been disclosed by Applicants or by recent research.

As discussed in the previous Office Action (26 September 2005), a 2-fold increase in gene amplification is not large and may be less likely to indicate disease (Hu, et al, 2003, Journal of Proteome Research 2:405-412), or may be sufficient (Applicant's Response, page 12). However, the type or magnitude of increase is not at issue in this case. All that is known about the PRO1182 genomic DNA is that it is increased in 3 samples of lung tumor tissue. It cannot be determined what the function of PRO1182 is in the tissues, and the fact that a minority of tumor tissues is stained confuses the issue. It is hard to conceive of a specific and substantial utility for a peptide encoded by a nucleic acid for which so little consistent data or information is given.

For example, what might be the connection between the normal tissue and the cancerous tissue that would provide clues to the PRO peptide's function?

In addition, Applicants assert that they are relying on the adipocyte glucose/FFA uptake assay (Example 149) for support of patentable utility (see Response, page 3, 20 January 2006). Applicants explain that the glucose/FFA assay is designed to determine whether a polypeptide is capable of modulating (either positively or negatively), the uptake of glucose or free fatty acids in adipocyte cells. They previously cited Tafuri et al. (Endocrinology 137(11) : 4706-4712, 1996), Sandouk et al. (endocrinology 133(1): 352-359, 1993), Goldwaser et al. (J Biol Chem 274(37): 26617-26624, 1999), Mueller et al. (Endocrinology 139(2) : 551-558, 1998), and Mueller et al. (Obesity Research 8(7): 530-539, 2000) to support the assertion that increasing glucose uptake by adipocyte cells is a hallmark of a number of therapeutically effective agents. Applicants argue that one of skill in the art would have reasonably accepted that various compounds, such as the peptide of PRO1182, are capable of modulating glucose uptake and thus have a substantial, practical, real-life utility. They contend that a variety of real-life utilities, such as treatments for glucose uptake-related diseases, including obesity and diabetes, are envisioned for PRO1182 peptide, based on the glucose/FFA uptake assay results disclosed in the instant Specification.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification of the instant application teaches that PRO1182 is positive as an *inhibitor* of glucose and FFA uptake by adipocytes (Example 158, page 530). Applicants reiterate this finding by stating at pg 8 of the previous Response (23 June 2005), "As PRO1182 resulted in

less then 0.5 the uptake of insulin control, PRO1182 tested positive as an inhibitor of glucose/FFA uptake in adipocyte cells." However, each of the references cited by Applicants teaches that the agents utilized in the assays *enhance* glucose uptake by adipocyte cells, not inhibit glucose uptake as asserted by the instant specification. Disorders such as obesity, diabetes, and hyper- or hypo-insulinemia are characterized by a reduction in the amount of glucose entering all cells, including adipocytes. For example, Tafuri et al. (1996, Endocrinology 137(11) : 4706-4712) and Sandouk et al. (1993, Endocrinology 133(1): 352-359) both describe how troglitazone and poiglitazone are members of the thiazolidinedione class of compounds and have been used to effectively treat non-insulin-dependent diabetes mellitus, the most common form of diabetes. Both compounds have been shown to function, at least in part, by increasing the number of cellular glucose transporters in order to facilitate increased glucose uptake. Goldwaser et al., (1999, J Biol Chem., 274(37): 26617-26624), using the rat adipocyte culture system, showed that vanadium ligand l-G1u (gamma) HXM potentiates the capacity of free vanadium ions to activate glucose uptake and glucose metabolism in rat adipocytes in vitro by 4-5 folds and to thus lower blood glucose levels in hyperglycemic rats. Similar assays are commonly used to identify potential anti-diabetic agents and to examine the regulatory mechanisms of important molecules involved in fat cell metabolism (Mueller et al., 1998, Endocrinology, 139(2): 551-558 and Mueller et al., 2000, Obesity Research, 8(7): 530-539).

The studies cited by the Applicants, as well as other studies teach that type II (non-insulin-dependent) diabetes mellitus is a clinical disorder of sugar and fat metabolism caused by an inability of insulin to promote sufficient glucose uptake into adipocyte tissue and striated muscle and to prevent glucose output from the liver. Therefore, as emphasized by Tafuri et al.,

Sandouk et al., Goldwaser et al., Mueller et al. 1998, and Mueller et al. 2000, one skilled in the art is searching for agents that will enhance glucose uptake into adipocyte cells. However, it is noted again that the Specification shows the PRO1182 polypeptide inhibits glucose uptake in adipocyte cells. If one skilled in the art were to administer the PRO1182 polypeptide encoded by the nucleic acid of the instant application to a patient with obesity, diabetes, or hyper- or hypo-insulinemia, the PRO1182 polypeptide would exacerbate the condition. Given the paucity of information, the data do not support the implicit conclusion of the specification that PRO1182 would be useful for the therapeutic treatment of disorders where the inhibition of glucose uptake by adipocytes would be beneficial, including for example, obesity, diabetes or hyper- or hypo-insulinemia. The proposed use of the claimed PRO1182 polypeptides is simply starting points for further research and investigation into potential practical uses of the polypeptides.

Furthermore, Tafuri et al., Sandouk et al., Goldwaser et al., Mueller et al. 1998, and Mueller et al. 2000 teach different methodologies for the measurement of glucose uptake in adipocyte cells as compared to the glucose assay of the instant specification. For instance, the instant specification teaches that "in a 96 well format, PRO polypeptides to be assayed are added to primary rat adipocytes, and allowed to incubate overnight" (page 8, Response 20 January 2006). Samples are taken at 4 and 16 hours and assayed for glycerol, glucose and FFA uptake. After the 16-hour incubation, insulin is added to the media and allowed to incubate for 4 hours. At this time, a sample is taken and glycerol, glucose and FFA uptake is measured. Media containing insulin without the PRO polypeptide is used as a positive reference control" (pg 512, lines 1-4). However, Sandouk et al. teach that 3T3-F442A cell monolayers were rinsed with PBS and incubated with assay medium for 15 min. Then, 0.5 Ci $_{D}$-[U-^{14}C]glucose was added for

15 min. After this incubation, the medium was aspirated; cells were rinsed, solubilized, neutralized, and counted for radioactivity (pg 353, col 1, first full paragraph). Mueller et al. 2000 disclose that aliquots of adipocytes are incubated with different concentrations of either metformin or vanadium at 24, 48, 72, and 96 hours with or without insulin (pg 532, the bottom of col 1 through col 2). Additionally, the papers cited by Applicants report results for the various samples of the glucose uptake assays. None of the references utilizes the same grading scale disclosed in the specification (pg 512, lines 4-6), but instead report dose-response curves. The instant specification does not report any specific cell numbers or statistical differences and there is no indication in the specification as to how much the PRO1182 inhibited glucose uptake as compared to control or whether the results were statistically significant.

In conclusion, the PRO1182 peptide of the instant application (made against SEQ ID NO: 357) is not supported by either a credible, specific and substantial ("real-world") asserted utility or a well-established utility. The peptide does not have a substantial utility because basic research is required to study the properties and activity of the polypeptide of SEQ ID NO: 357. Until some actual and specific significance can be attributed to the protein identified in the specification as PRO1182, the instant invention is incomplete. In the absence of knowledge of the biological significance of this protein, there is no immediately obvious patentable use for it. Since the instant specification does not disclose a "real world" use for PRO1182, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

Since the asserted utility for the PRO1182 peptide is not in currently available form, the asserted utility is not substantial.

35 USC § 112, first paragraph – Written Description.

The Written Description rejection is *maintained* for Claims 119-123. Claims 119-123 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The reasons for this rejection under *35 U.S.C. § 112, first paragraph,* are set forth at pp. 6-8 of the previous Office Action (26 September 2005). Briefly, the Applicants were not in possession of all or a significant number of polypeptides that have 80-99% homology to SEQ ID NO: 357 and still retain the function of SEQ ID NO: 357.

Applicants discuss the legal standards applied when evaluating Written Description, especially the requirement that the Specification must be evaluated by one of skill in the art (page 9, 23 June 2003). The examiner takes no issue with the discussion of general requirements for evaluating Written Description in this case. However, Applicants have not described or shown possession of all polypeptides 80-99% homologous to SEQ ID NO: 357, that still retain the function of SEQ ID NO: 357. Nor have Applicants described even *a representative number* of species that have 80-99% homology to SEQ ID NO: 357, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 357.

As discussed in the previous Office Action (26 September 2005) even a very skilled artisan could not envision the detailed chemical structure of all or a significant number of encompassed PRO1182 polypeptides, and therefore, would not know how to make or use them. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. The product itself is required. Recitation of the

phrase "wherein the peptide encoded by said nucleic acid inhibits the uptake of glucose or FFA (free fatty acids) by adipocyte cells," (amended claims), is not adequate to describe the polypeptides that have 80-99% homology to the PRO1182 polypeptides, since there was no reduction to practice to support the amended claims (i.e., no *variants* were tested in the glucose/FFA uptake test). Applicants made no variant polypeptides, and as recited in the current Written Description Guidelines, Applicants must have invented the subject matter that is claimed and must be in "possession" of the claimed genus (Federal Register, 2001, Vol. 66, No. 4, pages 1099-1111, esp. page 1104, 3rd column).

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire Later than SIX MONTHS from the mailing date of this final action.

Conclusion

No claims are allowed.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
30 March 2006

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER